proliferation in mammals by administering to a mammal in need thereof an effective amount of leptin or a mutein, fragment, or fusion protein thereof, or a leptin receptor agonist which has the ability to block cell proliferation.

It is noted with appreciation that the previous rejection of claims 2-9 and 28-39 under 35 USC 112, first paragraph, for enablement for a method of inhibiting tumor cell proliferation *in vivo* has been withdrawn.

Claims 2-8 and 28, 30-34 and 36-39 have been rejected under 35 USC 112, first paragraph, because the specification, while being enabling for leptin and leptin fusion proteins, does not reasonably provide enablement for leptin muteins, leptin receptor agonists or active fragments thereof as inhibitors of tumor cell proliferation. The examiner states that applicants' arguments have been drawn to written description guidelines, but that the present rejection is based on enablement and not written description. This rejection is respectfully traversed.

The enablement requirement of 35 USC 112 is discussed at section 2164 *et seq* of the MPEP. MPEP §2164.01 states that any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contains sufficient information regarding the subject matter of the

claims as to enable one skilled in the pertinent art to make and use the claimed invention. The question is whether the experimentation needed to practice the invention is undue or unreasonable. If the invention can be practiced without undue or unreasonable experimentation, the enablement requirement is considered to be met. The undue experimentation factors of In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) are set forth at MPEP §2164.01(a). These factors include:

(a) the breadth of the claims;

(b) the nature of the invention;

(c) the state of the prior art;

(d) the level of one of ordinary skill;

(e) the level of predictability in the art;

(f) the amount of direction provided by the inventor;

(g) the existence of working examples; and

(h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Here, the examiner takes the position that the scope of the claims is broader than the enabled disclosure with respect to muteins of a leptin, with respect to fragments of leptin, and with respect to leptin receptor agonists. Claim 28(b) defines a mutein of leptin as being one

> having at least 60% identity with the sequence of a leptin and has the ability to block cell proliferation

or one

> having a sequence encoded by a nucleic acid which hybridizes to a nucleic acid which encodes leptin under stringent conditions and has the ability to block cell proliferation.

By emphasizing that the rejection is an enablement rejection and not based on written description requirement, the examiner has effectively conceded that the present inventors were in the possession of all of the muteins which fall within this definition. Thus, the examiner effectively concedes that applicant was in possession of the necessary common attributes possessed by members of the genus, particularly since the claim requires that each member have the attribute of the ability to block cell proliferation. As indicated in the written description guidelines discussed in applicants' response of July 30, 2001, the examiner must be effectively conceding that, the single species disclosed in the examples is representative of the genus because all members have at least 60% structural identity with the reference compound, and due to the presence of an assay which applicant provides for identifying all of the at least 60% identical variants of leptin which are capable of the specified activity. These concessions are a good starting

point for analysis of the Wands factors to determine whether the experimentation is undue.

With respect to the breadth of claims, claim 28 is substantially broader than leptin. The claimed scope is necessary in order to reasonably cover the invention. In Section 2164.08 relating to enablement commensurate in scope with the claims, the MPEP quotes the following from In re Goffe, 191 USPQ 429, 431 (CCPA 1976):

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

It should be noted that the definition of fragment at claim 28(c) also requires that the fragment have the ability to block cell proliferation and the recitation of leptin receptor agonist at claim 28(e) again requires that such agonist have the ability to block cell proliferation. In view of the stated activity and the direction in the specification, which will be discussed below, the breadth is not unduly broad and the experimentation to find everything within the scope of these claims would not be undue.

As to the nature of the invention, this is a therapeutic method and applicant concedes that there is not

100% predictability in this field. However, this does not mean that an applicant must be limited to exemplified embodiments. As long as it is shown that the experimentation to determine what falls within the claim is not undue, the enablement requirement is met. As discussed below, the experimentation is not undue.

As to the state of the prior art, there is no close prior art. The reference cited by the examiner here is not available as a reference because of its date. Thus, there is no prior art reason for limiting the scope of the claims.

As to the level of one of ordinary skill, therapeutic inventions, and particularly ones involving biotechnology, involve a very high level of ordinary skill. Because of this extremely high level of ordinary skill, even complex experimentation is not necessarily undue or unreasonable.

The next two Wands factors, the level of the predictability in the art and the amount of direction provided by the inventor, go hand in hand. As discussed above, the examiner is correct that it may not be entirely predictable what specific changes to the protein might entail insofar as the properties of that protein are concerned. However, the present claim always requires that the result of the mutation have the ability to block cell proliferation, i.e., by

definition the activity must be retained. The present specification states at page 8, lines 27-31:

> Thus, it can be determined whether any given mutein has substantially the same activity as leptin by means of routine experimentation comprising subjecting such a mutein, e.g., to a simple cell proliferation assay, as a mutein which blocks cell proliferation retains sufficient activity of leptin and therefore has at least one of the disclosed utilities of leptin and thus has substantially similar activity thereto.

Furthermore, substantial guidance is provided in the present specification as to preferred substitutions which would be expected to retain the activity of the base compound, i.e., leptin. Note, for example, page 9, line 4, through page 13, line 7. The examples in the present specification, such as examples 1-4, show well-known cell proliferation assays. Indeed, four different cell proliferation assays are shown. These are simple tests which may be done in 96-well plates so that many experiments can be done at one time. Accordingly, it is apparent that there is substantial direction provided in the specification about how to do these simple cell proliferation assays. This is all that is necessary to do in order to determine whether any given mutein having at least 60% identity with the sequence of a leptin has the ability to block cell proliferation. The same is true with respect to testing of muteins having a sequence encoded by a nucleic acid which hybridizes to a nucleic acid which encodes leptin under

stringent conditions, fragments and leptin receptor agonists. Accordingly, substantial direction is provided by the specification.

As far as working examples are concerned, as discussed above, many working examples of cell proliferation assays are given in the specification and the effect of leptin in these assays is provided in working examples. While there are no working examples given in the specification for muteins, fragments and other leptin receptor agonists, the guidance of the specification explains how to determine whether any given compound falls within the scope of the claims, and therefore additional working examples are not necessary.

Finally, the last Wands factor is the quantity of experimentation needed to make or use the invention based on the content of the disclosure. It is true that substantial experimentation will be necessary. However, as stated at MPEP §2164.06, the test is not merely quantitative since a considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Time and expense are not the controlling factors. Procedures for making variants of leptin which have at least 60% identity with the

sequence of leptin are conventional in the art. The assays involved to determine whether any such mutein has the ability to block cell proliferation is routine as is disclosed in the specification and discussed above. All of the claimed muteins must possess the specified activity of being able to block cell proliferation. There is a reduction to practice of the single disclosed species of leptin. The fact that any single amino acid change might have a profound effect or no effect, does not really represent the state of the art. Here, a simple cell proliferation assay is provided in the specification and so any given mutein can readily be tested without undue experimentation. Thus, applicant needs not rely upon predictability with respect to changes, but is relying on testing in the simple assay described in the specification which can be carried out in large numbers at the same time.

The level of skill in the art is high and the assay is simple and can be conducted with many different mutein sequences at the same time. Thus, while substantial experimentation may be needed to establish that any given sequence falls within the scope of the claim, i.e., meets the functional requirement of blocking cell proliferation, such experimentation is not undue or unreasonable.

The same is true with respect to fragments. Fragments can be made by removing one amino acid at a time

from either end and testing for activity using the simple assays described in the specification and discussed above. Once the activity is lost, it would not be expected that smaller fragments would be operable. Thus, the amount of experimentation needed to find fragments is even less than that needed to find muteins.

The same is true with respect to leptin receptor agonists. Miscellaneous libraries can be readily and simply tested using the leptin receptor to determine if they bind to the receptor and then another simple assay will determine whether those that bind to the receptor have receptor agonist activity. If so, they can then be tested for the ability to block cell proliferation. Again, this would not involve undue experimentation as it is well within the skill of the art to find leptin receptor agonists once it is known that such agonists are useful for treating tumors in mammals or for inhibiting tumor cell proliferation in mammals.

For all of these reasons, reconsideration and withdrawal of this rejection with respect to the full scope of claim 28 are respectfully urged.

Claim 33 should be considered in its own right as the number of fragments of leptin is a reasonable number which can be tested using the simple assay disclosed in the present specification without undue experimentation, particularly in

view of the fact that they may be carried out with multitudes of fragments at the same time. Furthermore, those of ordinary skill in the art would know to go about it in a systematic way such as by removing one amino acid residue at a time from either end, until the fragment is so small as to no longer have activity when testing each in the simple disclosed assays. Accordingly, certainly claim 33 would not involve undue experimentation to determine which fragments fall within the scope of claim 33. Reconsideration and withdrawal of the rejection, particularly with respect to claim 33, are therefore also respectfully urged.

Claims 30, 37, 38 and 39 should also be considered on their own merits. Claim 39 specifies that the active agent is a mutein of leptin having at least 90% identity with the sequence of a leptin and has the ability to block cell proliferation. Certainly, the experimentation would not be unreasonable to test muteins with such a large identity with leptin, i.e., 90%. It is reasonably predictable that with such a relatively small amount of variation that such muteins would retain activity. But regardless of such predictability, the simple and rapidly performed assays disclosed in the specification can be conducted to establish that the ability to block cell proliferation has not been lost. Thus, it would not involve undue experimentation to determine muteins which

retain 90% identity with the sequence of a leptin and have the ability to block cell proliferation. If claim 39 is found to be enabled, then claim 38 should also be enabled because approximately the same amount of additional experimentation as has been previously conducted to determine 90% identity can also reasonably be conducted in order to determine whether muteins of 80% identity retain the ability to block cell proliferation. By extension, claims 37 and 30 should also be considered to be based on an enabled disclosure as the experimentation is not undue.

For all of these reasons, reconsideration and withdrawal of this rejection with respect to all of claims 2-8, 28, 30-34 and 36-39 are respectfully urged.

Claims 2-9, 28 and 29 have been rejected under 35 USC 102(a) as being anticipated by Rubinstein. This rejection is respectfully traversed.

The examiner's attention is invited to the fact that the present application claims priority from Israel application 120,733 filed April 29, 1997. The Rubinstein publication has a date of November 1997. Thus, if the present claims are entitled to the effective filing date of applicant's Israeli priority, then the Rubinstein abstract is not available as a reference. As the Israel priority application was filed in Israel in the English language, the

examiner can readily determine that the present claims are entitled to the effective filing date thereof. Indeed, the examiner's attention is invited to the International Preliminary Examination Report prepared by the International Preliminary Examining Authority with respect to this case, a copy of which has been made of record in the present application. The international examiner analyzed whether applicant was entitled to its priority date when considering this same abstract, which the international examiner called D1, and stated:

> D1, 5th Ann. Conf. Int. Cytokine Soc. South Lake Tahoe, 9(11), 9-13/11/97, Nevada USA, pp 953, Rubinstein M. et al., an intermediate document, discloses the inhibition of growth-factor induced cell proliferation by leptin (cf. the whole abstract). Moreover, D1 points at the possible treatment of breast tumor cells and tumors originating from other tissues due to its cell proliferation inhibiting effects. However, D1 is dated 11/97 and has been published after the priority date of the present application. As the use of leptin for both the inhibition of the growth factor induced cell proliferation as well as the inhibition of breast cancer are disclosed in the priority document (Israel application no. 120,737), D1 cannot prejudice the present subject-matter.

For these reasons, Rubinstein is not available as a reference. Reconsideration and withdrawal of this rejection are therefore respectfully urged.